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The chlorophyll metabolite phytanic acid is a natural rexinoid – potential for treatment and prevention of diabetes

M. F. McCarty

Pantox Laboratories, San Diego, USA

Summary Synthetic ligands of the retinoid X receptor (RXR) have shown antidiabetic activity in mice, apparently owing to the fact that they stimulate the transcriptional activity of PPAR-gamma/RXR heterodimers, much like thiazolidinedione drugs. The chlorophyll metabolite phytanic acid has been shown to be a natural ligand for RXR, active in concentrations near its physiological levels. It is thus reasonable to suspect that phytanic acid may have utility for treatment and prevention of human type 2 diabetes. Phytanic acid may mimic or complement various effects of conjugated linoleic acids, which have been shown to activate PPAR-gamma/RXR and prevent rodent diabetes. Administration of hydrolyzed chlorophyll may represent the most cost-effective strategy for raising human tissue levels of phytanic acid. © 2001 Harcourt Publishers Ltd

PHYTANIC ACID IS AN RXR LIGAND

The therapeutic efficacy of thiazolidinediones in diabetes stems from their ability to selectively activate PPAR-gamma/RXR heterodimer transcription factors in adipocytes and skeletal muscle; these drugs are potent PPAR-gamma ligands (1,2). Recently, agents which are selective ligands for the retinoid X receptor (RXR) – dubbed 'rexinoids' – have been shown to stimulate the transcriptional activity of PPAR-gamma/RXR in mouse adipocytes as well as in 3T3-L1 preadipocytes, in which they function much like thiazolidinediones, promoting differntiation in preadipocytes and potentiating insulin sensitivity (3,4). In mouse models of type 2 diabetes, synthetic rexinoids show antidiabetic effects comparable to those seen with thiazolidinediones, and the benefits of joint administration of rexinoids with thiazolidinediones are greater than those achievable with either agent administered separately (3).

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Correspondence to: **M. F. McCarty**, Pantox Laboratories, 4622 Santa Fe Street, San Diego, CA 92109, USA

Two recent reports indicate that phytanic acid, a saturated diterpene that is a prominent natural metabolite of chlorophyll, found preformed in dairy fat, beef fat, and fish oil, is a potent agonist for RXR, displacing the binding of 9-cis-retinoic acid to this receptor with a K_i of about 4 μM (5,6). (9-cis-retinoic acid is the only previously characterized natural agonist for this receptor; Lemotte and collegues show that, when properly coiled, the structure of phytanic acid is very similar to that of 9-cis-retinoic acid (5).) (5) Phytenic acid, the immediate biosynthetic precursor of phytanic acid, has a similar affinity for RXR (6). It has been suggested that, inasmuch as natural concentrations of phytanic acid in human serum are in the low micromolar range (7) – close to the affinity of this compound for RXR – phytanic acid may play a quasi-essential physiological role in supporting RXR function (6). (In contrast, natural concentrations of 9-cis-retinoic acid are far too low for this agent to serve as a physiological activator of RXR.)

If phytanic acid activates PPAR-gamma/RXR heterodimers in a manner akin to synthetic rexinoids, it should follow that phytanic acid will have antidiabetic activity similar to that of the thiazolidinediones. The

current published literature does not evaluate this possibility.

ANALOGIES TO CONJUGATED LINOLEIC ACIDS

Conjugated linoleic acids (CLA) have recently been shown to be PPAR-gamma agonists in rat adipocytes, and, in vivo, can normalize impaired glucose tolerance in Zucker diabetic fatty rats (8). This suggests that CLA and phytanic acid could exert complementary antidiabetic activity by promoting strong activation of the PPAR-gamma/RXR heterodimer. Intriguingly, CLA and phytanic acid both occur in the diet primarily as minor constituents of dairy and beef fat.

In rodent studies, CLA exerts a fascinating range of activities: it is anticarcinogenic and tumor retardant, hypolipidemic, antidiabetic, antiinflammatory, and also decreases body fat (8–24). It seems likely that many of these effects are mediated by transcription factor activation. In addition to PPAR-gamma, CLA activates PPAR-alpha, the hepatic inducer of peroxisomal enzymes (25,26). Phytanic acid likewise possesses this activity (27,28) – a reflection of the fact that its catabolism is exclusively peroxisomal (29). It would be of great interest to determine whether phytanic acid can duplicate and perhaps potentiate various of the beneficial effects of CLA. In light of the fact that CLA can slow the growth of certain human tumors in nude mice (16,17), it is relevant to note that synthetic rexinoids have been shown to induce apoptosis or differentiation in various neoplastic cell lines (30–32).

FEASIBILITY AND SAFETY CONSIDERATIONS

If phytanic acid shows promise in rodent studies, the logistical feasibility of providing adequate amounts of this compound for human use must be addressed. Currently, commercially available phytanic acid is extremely expensive. However, its biosynthetic precursor phytol is relatively inexpensive, as it can be derived from chlorophyll by hydrolysis of an ester bond (6). When humans as well as rodents are fed free phytol, a high proportion is absorbed and converted in vivo to phytanic acid (33–36); this conversion is catalyzed by hepatic microsomes (37). However, in humans and rodents, consumption of intact chlorophyll gives rise to little phytanic acid, apparently because digestive enzymes do not cleave the ester bond in chlorophyll (38–40). (In contrast, in ruminants, rumenal bacteria can accomplish this hydrolysis and liberate free phytol for absorption; this accounts for the significant level of phytanic acid in the tissue and milk fat of cows (41). Analogously, rumen bacterial activity is primarily responsible for the significant CLA content of bovine fat.) These considerations suggest that hydrolyzed chlorophyll; administered as a nutritional supplement, could do an effective job of raising human tissue levels of phytanic acid, at an affordable cost.

To date, the chief research interest in phytanic acid stems from the fact that, in heritable disorders of peroxisomal function, such as Refsum's disease, Zellwenger's syndrome, and adrenoleukodystrophy, phytanic acid catabolism is severley impaired, such that tissue levels of this fatty acid rise dramatically; for example, in untreated Refsum's disease, phytanic acid may constitute over 20% of total tissue lipids (5,29,34). This gross excess of phytanic acid is thought to mediate much of the pathology associated with these syndromes, and is clearly the chief culprit in Refsum's disease. In rodents, a diet with 5% phytol or phytanic acid leads to comparable gross elevations of tissue phytanic acid – presumably because hepatic capacity for peroxisomal catabolism is overwhelmed at these extreme intakes – and results in weight loss and death (34). (Dietary intakes of 0.5–1% are tolerated.) There is no evidence that overactivation of RXR has anything to do with the pathogenic impact of greatly excessive tissue levels of phytanic acid, although this possibility has been raised (5). Despite these concerns, it is reasonable to expect that, in individuals possessed of normal peroxisomal function, moderate daily doses of phytol or phytanic acid would be well tolerated, but could be sufficient to achieve an increase in tissue phytanic acid levels that is physiologically meaningful vis a vis RXR activation.

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